

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1-120. (canceled)

121. (previously presented) A human monoclonal antibody reactive with the TSH receptor; or a fragment of a human monoclonal antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor.

122-125. (canceled)

126. (previously presented) The monoclonal antibody or fragment of claim 121, wherein the monoclonal antibody or fragment has an inhibitory activity of at least 15 units of International Standard NIBSC 90/672 per mg.

127. (previously presented) The monoclonal antibody or fragment of claim 126, wherein the monoclonal antibody or fragment has an inhibitory activity of at least 120 units of International Standard NIBSC 90/672 per mg.

128. (canceled)

129. (previously presented) The monoclonal antibody or fragment of claim 121, wherein the monoclonal antibody or fragment has a stimulatory activity with respect to cAMP production of at least 30 units of International Standard NIBSC 90/672 per mg.

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

130. (previously presented) The monoclonal antibody or fragment of claim 129, wherein the monoclonal antibody or fragment has a stimulatory activity with respect to cAMP production of at least 240 units of International Standard NIBSC 90/672 per mg.

131-132. (canceled)

133. (previously presented) The monoclonal antibody or fragment of claim 126, wherein the monoclonal antibody or fragment has a stimulatory activity with respect to cAMP production of at least 30 units of International Standard NIBSC 90/672 per mg.

134. (previously presented) The monoclonal antibody or fragment of claim 121, wherein the monoclonal antibody or fragment comprises a VH domain as shown in Seq. ID NO: 1, or one or more VH CDRs selected from SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4.

135. (previously presented) The monoclonal antibody or fragment of claim 134, wherein the monoclonal antibody or fragment further comprises an antibody VL domain as shown in SEQ ID NO: 6, or one or more VL CDRs selected from SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.

136. (previously presented) The monoclonal antibody or fragment according to claim 121, which is a fragment of a human monoclonal antibody reactive with the TSH receptor and has an inhibitory activity with respect to TSH binding to the TSH receptor of at least 30 units of International Standard NIBSC 90/672 per mg.

137. (previously presented) The monoclonal antibody or fragment according to claim 121, which is a fragment of a human monoclonal antibody reactive with the TSH receptor and has a

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

stimulatory activity with respect to cAMP production by cells expressing TSH of at least 50 units of International Standard NIBSC 90/672 per mg.

138-156 (canceled)

157. (withdrawn) The process of claim 162, wherein the subject has TSH receptor antibody activity greater than 0.1 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

158. (withdrawn) The process of claim 157, wherein the subject has TSH receptor antibody activity greater than 0.2 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

159. (withdrawn) The process of claim 158, wherein the subject has TSH receptor antibody activity in the range of 0.3 to 0.5 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

160-161. (canceled)

162. (withdrawn) A process for making a human monoclonal antibody reactive with TSH receptor comprising the steps of:

(a) isolating lymphocytes from a subject having TSH receptor antibody activity greater than 0.1 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of cAMP production by cells expressing the TSH receptor or a subject having TSH antibody

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

activity 0.04 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor;

- (b) immortalizing the isolated lymphocytes,
- (c) cloning the immortalized lymphocytes to produce an immortalized colony secreting a human monoclonal antibody reactive with the TSH receptor, and
- (d) isolating or purifying a monoclonal antibody from the immortalized colony, wherein said antibody is selected to have the characteristics of TSH receptor antibodies present in serum of patients with hyperthyroid Graves' disease with respect to inhibition of TSH binding to the TSH receptor and with respect to stimulation of cAMP production by cells expressing the TSH receptor.

163. (withdrawn) The process of claim 162, wherein the subject has TSH receptor antibody activity greater than 0.3 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of cAMP production by cells expressing the TSH receptor.

164. (withdrawn) The process of claim 163, wherein the subject has TSH receptor antibody activity greater than 0.5 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of cAMP production by cells expressing the TSH receptor.

165. (withdrawn) The process of claim 164, wherein the subject has TSH receptor antibody activity in the range of 0.5 to 1 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of cAMP production by cells expressing the TSH receptor.

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

166. (withdrawn) The process of claim 162, wherein the lymphocytes are isolated from peripheral blood, thyroid tissue, spleen tissue, lymph nodes or bone marrow.

167. (withdrawn) The process of claim 162, wherein the isolated lymphocytes are immortalized by infection with Epstein Barr virus, and the thus immortalized lymphocytes are fused with a mouse or human cell line to form the immortalized colony.

168. (withdrawn) A method for screening for autoantibodies to TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, being susceptible to, having or recovering from an autoimmune disease with an immune reaction to the TSH receptor, said method comprising the steps of:

- (a) obtaining a sample of body fluid from said subject;
- (b) providing a pair of binding molecules, said pair comprising a first molecule comprising a binding partner, wherein said binding partner is
  - a human monoclonal antibody reactive with the TSH receptor; or
  - a fragment of a human monoclonal antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor; or
  - a human recombinant antibody reactive with the TSH receptor; or
  - a fragment of a human recombinant antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor; and

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

a second molecule comprising a binding region with which the first molecule interacts, said second molecule being further capable of interacting with autoantibodies to the TSH receptor that may be present in the sample;

(c) contacting the sample with the pair of binding molecules so as to permit the second molecule to interact with the first molecule or with autoantibodies to the TSH receptor that may be present in the sample; and

(d) monitoring the interaction of the second molecule with autoantibodies in the sample, thereby providing an indication of the presence of autoantibodies to the TSH receptor in the sample.

169. (withdrawn) The method of claim 168, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable.

170. (withdrawn) The method of claim 168, wherein the first molecule has an affinity for the TSH receptor of  $10^{10}$  molar<sup>-1</sup> or greater.

171. (withdrawn) The method according to claim 168, wherein the second molecule comprises full length TSH receptor, or one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSH receptor.

172. (canceled)

173. (withdrawn) A method for assaying for TSH or related ligands comprising the steps of

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

- (a) obtaining a sample to be assayed for TSH or related ligands;
- (b) providing a pair of binding molecules, said pair comprising a first molecule comprising a binding partner, wherein said binding partner is
  - a human monoclonal antibody reactive with the TSH receptor; or
  - a fragment of a human monoclonal antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor; or
  - a human recombinant antibody reactive with the TSH receptor; or
  - a fragment of a human recombinant antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor;
  - and a second molecule comprising a binding region with which the first molecule interacts, said second molecule being further capable of interacting with TSH or related ligands that may be present in the sample;
- (c) contacting the sample with the pair of binding molecules so as to permit the second molecule to interact with the first molecule or with TSH or related ligands that may be present in the sample; and
- (d) monitoring the interaction of the second molecule with TSH or related ligands in the sample, thereby providing an indication of the presence of TSH or related ligands in the sample.

174. (withdrawn) A method for evaluating a potential binding partner for the TSH receptor comprising the steps of:

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

(a) providing a pair of binding molecules, said pair comprising a first molecule comprising a binding partner, wherein said binding partner is

a human monoclonal antibody reactive with the TSH receptor; or  
a fragment of a human monoclonal antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor; or

a human recombinant antibody reactive with the TSH receptor; or  
a fragment of a human recombinant antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor;

and a second molecule comprising a binding region with which the first molecule interacts;

(b) contacting the potential binding partner to be evaluated with said first molecule and said second molecule so as to permit the second molecule to interact with either the potential binding partner to be evaluated or the first molecule; and

(c) monitoring the interaction of the second molecule with the potential binding partner to be evaluated, wherein competition with the binding of the first molecule to the second molecule indicates that the potential binding partner being evaluated binds to the TSH receptor.

175. (withdrawn) A method for identifying an epitope of the TSH receptor, comprising the steps of:

(a) contacting a binding partner with a full length TSH receptor, or a fragment thereof, and allowing interaction of the binding partner with the full length TSH receptor, or a fragment thereof, wherein said binding partner is



Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

a human monoclonal antibody reactive with the TSH receptor; or  
a fragment of a human monoclonal antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor; or

a human recombinant antibody reactive with the TSH receptor; or  
a fragment of a human recombinant antibody reactive with the TSH receptor, wherein the monoclonal antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor; and

(b) identifying the amino acids in the full length TSH receptor, or fragment thereof, with which the binding partner interacts.

176-178. (canceled)

179. (withdrawn) A method for treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to the subject a therapeutically effective amount of a binding partner according to claim 121.

180-181. (canceled)

182. (withdrawn) The method of claim 179, wherein the binding partner inhibits interaction of the TSH receptor with autoantibodies present in the subject's circulation, and wherein interaction of the TSH receptor and autoantibodies is responsible for or associated with said autoimmune disease.

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

183. (withdrawn) The method of claim 179, wherein the autoimmune disease is disease of the retro-orbital tissues of the eye.

184. (withdrawn) A method of stimulating thyroid or other tissue containing the TSH receptor in a subject in need of such stimulation, comprising administering to the subject a diagnostically or therapeutically effective amount of a binding partner according to claim 121.

185. (withdrawn) The method of claim 184, further comprising the step of administering an additional agent, different from the binding partner, capable of stimulating the TSH receptor.

186. (withdrawn) The method of claim 185, wherein the additional agent is selected from the group consisting of recombinant human TSH and bioactive variants, analogs, derivatives and fragments thereof.

187-188. (canceled)

189. (withdrawn) In combination, a binding partner according to claim 121 that stimulates the TSH receptor, and an agent different from the binding partner capable of stimulating TSH receptors for simultaneous or sequential use in stimulating tissue containing the TSH receptor.

190. (withdrawn) The combination of claim 189, wherein the agent is selected from the group consisting of recombinant human TSH and bioactive variants, analogs, derivatives and fragments thereof.

191. (withdrawn) The combination of claim 189, wherein the agent acts independently of binding to the TSH receptor.

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

192. (withdrawn) In combination, a binding partner according to claim 121 and an agent different from the binding partner or further binding partner, said binding partner and said agent each being capable of inactivating or rendering TSH receptors unresponsive to stimulation by TSH, TSH receptor autoantibodies or other stimulators, for simultaneous or sequential use.

193-194 (canceled)

195. (withdrawn) A process of preparing a preparation required to comprise a defined concentration of TSH receptor antibody or antibodies, which process comprises providing a binding partner according to claim 121 as a suitable preparation having the required defined concentration of TSH receptor antibody or antibodies.

196-197. (canceled)

198. (previously presented) The monoclonal antibody or fragment of claim 121, wherein the binding partner has an affinity for TSH receptor of at least  $10^{10} \text{ M}^{-1}$ .

199. (canceled)

200. (previously presented) An isolated and/or purified binding partner comprising an antibody VH domain as shown in SEQ. ID NO: 1.

201. (currently amended) The binding partner of claim 200, further comprising an antibody VL domain as shown in SEQ. ID No: 6, or one or more VL CDRs selected from SEQ. ID NO: 7, SEQ. ID NO: 8, and SEQ. ID NO: 9.

Application No. 10/537,280  
Amendment Dated: January 3, 2011  
Response to Office Action mailed April 6, 2010 and  
Notice of Non-Compliant mailed December 14, 2010.

202. (previously presented) An isolated and/or purified binding partner that binds to TSH receptor comprising one or more VH CDRs selected from SEQ. ID NO: 2, SEQ. ID NO: 3, and SEQ. ID NO: 4, and further comprising an antibody VL domain as shown in SEQ. ID No: 6, or one or more VL CDRs selected from SEQ. ID NO: 7, SEQ. ID NO: 8, and SEQ. ID NO: 9.

203. (canceled)

204. (previously presented) A human recombinant antibody reactive with the TSH receptor; or a fragment of a human recombinant antibody reactive with the TSH receptor, wherein the recombinant antibody or fragment inhibits TSH binding to the TSH receptor and stimulates cAMP production by cells expressing the TSH receptor.

205. (previously presented) The recombinant antibody or fragment of claim 204, wherein the recombinant antibody or fragment has an inhibitory activity of at least 15 units of International Standard NIBSC 90/672 per mg.

206. (previously presented) The recombinant antibody or fragment of claim 205, wherein the recombinant antibody or fragment has an inhibitory activity of at least 120 units of International Standard NIBSC 90/672 per mg.

207. (previously presented) The recombinant antibody or fragment of claim 204, wherein the recombinant antibody or fragment has a stimulatory activity with respect to cAMP production of at least 30 units of International Standard NIBSC 90/672 per mg.

Application No. 10/537,280

Amendment Dated: January 3, 2011

Response to Office Action mailed April 6, 2010 and

Notice of Non-Compliant mailed December 14, 2010.

208. (previously presented) The recombinant antibody or fragment of claim 205, wherein the monoclonal antibody or fragment has a stimulatory activity with respect to cAMP production of at least 240 units of International Standard NIBSC 90/672 per mg.

209. (previously presented) The recombinant antibody or fragment of claim 205, wherein the recombinant antibody or fragment has a stimulatory activity with respect to cAMP production of at least 30 units of International Standard NIBSC 90/672 per mg.

210. (previously presented) The recombinant antibody or fragment of claim 210, wherein the monoclonal antibody or fragment comprises a VH domain as shown in Seq. ID NO: 1, or one or more VH CDRs selected from SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4.

211. (previously presented) The recombinant antibody or fragment of claim 210, wherein the monoclonal antibody or fragment further comprises an antibody VL domain as shown in SEQ ID NO: 6, or one or more VL CDRs selected from SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.

212. (previously presented) The recombinant antibody or fragment of claim 204, wherein the recombinant antibody or fragment has an inhibitory activity of at least 30 units of International Standard NIBSC 90/672 per mg.

213. (previously presented) The recombinant antibody or fragment of claim 204, wherein the recombinant antibody or fragment has a stimulatory activity with respect to cAMP production of at least 50 units of International Standard NIBSC 90/672 per mg.